

CLAIMS

1. A method for haplotyping, comprising:
analyzing a first polymorphic locus of a nucleic acid within a sample by
specifically capturing the nucleic acid on a surface wherein the step of capturing the
5 nucleic acid on the surface identifies a first allele of a first SNP of the polymorphic
locus,
analyzing a second allele of the first SNP of the polymorphic locus by
specifically capturing the nucleic acid on a surface wherein the step of capturing the
nucleic acid on the surface identifies the second allele of the first SNP of the
10 polymorphic locus,
separately analyzing a second SNP of a polymorphic locus of the nucleic acid
sample to identify both alleles of the second SNP, and
determining the haplotype based on the identification of each allele of each SNP.
- 15 2. The method of claim 1, wherein the second SNP is analyzed using a method
selected from the group consisting of hybridization, primer extension, MALDI TOF, and
HPLC.
- 20 3. The method of claim 1, wherein the nucleic acid is captured by hybridization
with an ASO, and wherein the ASO is fixed to a surface.
- 25 4. The method of claim 3, wherein a first ASO complementary to a first allele of
the first SNP and a second ASO complementary to a second allele of the first SNP are
hybridized to the surface and are used to capture the nucleic acid.
5. The method of claim 1, wherein the surface is a multiwell dish.
6. The method of claim 1, wherein the surface is a chip.
- 30 7. The method of claim 1, wherein the surface is a slide.
8. The method of claim 1, wherein the surface is a bead.

9. The method of claim 4, wherein each ASO corresponding to an allele of the first SNP further includes a spacer sequence.

5 10. The method of claim 9, wherein the spacer sequence is selected from the group consisting of a poly-T, poly-A, poly-C, and poly-G.

11. The method of claim 2, wherein the second SNP is analyzed by hybridization of the nucleic acid sample with an ASO complementary to a first allele of the second
10 SNP and an ASO complementary to a second allele of the second SNP.

12. The method of claim 11, wherein each of the ASOs corresponding to an allele of the second SNP is hybridized independently to the nucleic acid sample.

13. The method of claim 11, wherein at least one of the ASOs complementary to
15 an allele of the first SNP and at least one of the ASOs complementary to an allele of the second SNP contains a fluorescent label or quencher, the fluorescent label or quencher of the two ASOs, being distinct from one another.

14. The method of claim 2, wherein the alleles of the second SNP are analyzed
20 simultaneously with one another.

15. The method of claim 1, wherein each of the ASOs complementary to an allele of the first SNP and each of the ASOs complementary to an allele of the second
25 SNP contains a fluorescent label or quencher, the fluorescent label or quencher of each of the four ASOs, being distinct from one another.

16. The method of claim 1, wherein the nucleic acid sample is prepared by PCR amplification of a polymorphic locus from a genomic DNA sample.

30 17. The method of claim 1, wherein the nucleic acid sample is a reduced complexity genome.

18. The method of claim 1, wherein the nucleic acid sample is labeled with a first label.

5 19. The method of claim 1, wherein the presence of one set of alleles at the polymorphic locus is associated with a disease and the haplotyping method is performed to identify predisposition to the disease.

10 20. The method of claim 1, further comprising analyzing a third SNP of a polymorphic locus of the nucleic acid sample to identify both alleles of the third SNP, and determining the haplotype based on the identification of each allele of each SNP.

15 21. The method of claim 1, further comprising analyzing a fourth SNP of a polymorphic locus of the nucleic acid sample to identify both alleles of the fourth SNP, and determining the haplotype based on the identification of each allele of each SNP.

22. The method of claim 1, wherein the analysis of the first and second SNPs are performed simultaneously.

20 23. The method of claim 1, wherein the nucleic acid is captured by a method selected from the group consisting of OLA, primer extension, and binding partner-ASO hybridization.

25 24. The method of claim 1, wherein the capture steps for the analysis of the first and second alleles of the first SNP are performed using different capture methods.

25. The method of claim 1, wherein the nucleic acid sample is an RNA genome.

26. The method of claim 1, wherein the RNA genome is made from cDNA.

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27. The method of claim 1, wherein the nucleic acid sample is genomic DNA.

28. The method of claim 1, wherein the nucleic acid sample is a mitochondrial genome.

29. A method for haplotyping, comprising:

- 5 analyzing a genotype of a first SNP of a polymorphic locus of a nucleic acid within a sample in solution by detecting the presence or absence of a first labeled probe which specifically identifies a first putative allele of the SNP and detecting the presence or absence of a second labeled probe which specifically identifies a second putative allele of the SNP,
- 10 separating the nucleic acid sample based on the genotype of the first SNP, analyzing a second SNP of the polymorphic locus of the separated nucleic acid samples to identify the haplotype of the nucleic acid.

30. The method of claim 29, wherein the analysis of the first SNP is performed
15 using fluorescence detection.

31. The method of claim 30, wherein the nucleic acid sample is separated using a flow cytometry.

20 32. The method of claim 29, wherein the second SNP is analyzed using a method selected from the group consisting of hybridization, primer extension, MALDI TOF, and HPLC.

25 33. The method of claim 29, wherein the nucleic acid sample is prepared by PCR amplification of a polymorphic locus from a genomic DNA sample.

34. The method of claim 29, wherein the nucleic acid sample is a reduced complexity genome.

30 35. The method of claim 29, wherein the second SNP is identified using a capture reaction and wherein the nucleic acid is captured by a method selected from the group consisting of OLA, primer extension, and binding partner-ASO hybridization.

36. The method of claim 29, wherein the nucleic acid sample is an RNA genome.

5 37. The method of claim 29, wherein the RNA genome is made from cDNA.

38. The method of claim 29, wherein the nucleic acid sample is genomic DNA.

10 39. The method of claim 29, wherein the nucleic acid sample is a mitochondrial genome.

40. A method for haplotyping, comprising:

labeling first and second SNPs of a polymorphic locus of a nucleic acid within a sample in solution with a first, second, third, and fourth labeled probe which specifically
15 identifies a first and second putative allele of the first SNP and a first and second putative allele of the second SNP respectively,

separating the labeled nucleic acid sample into single nucleic acid molecules,
detecting the presence or absence of the first, second, third, and fourth labeled probes on the single nucleic acid molecules to identify the haplotype of the nucleic acid.

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41. The method of claim 40, wherein the probes are labeled with fluorescence molecules.

25 42. The method of claim 41, wherein each of the fluorescent molecules of the labeled probes is spectrally distinct.

43. The method of claim 40, wherein the nucleic acid sample is prepared by PCR amplification of a polymorphic locus from a genomic DNA sample.

30 44. The method of claim 40, wherein the nucleic acid sample is a reduced complexity genome.

45. The method of claim 40, wherein the nucleic acid sample is an RNA genome.

46. The method of claim 40, wherein the RNA genome is made from cDNA.

47. The method of claim 40, wherein the nucleic acid sample is genomic DNA.

48. The method of claim 40, wherein the nucleic acid sample is a mitochondrial genome.

49. A method for haplotyping, comprising:

performing four hybridization reactions on a nucleic acid sample, each of the four hybridization reactions involving one labeled probe specific for one allele of one of two SNPs, each of the labeled probes labeled with a spectrally distinct label and wherein each label on the probe specific for a first of the two SNPs is a spectral pair with the label on each probe specific for the second of the two SNPs,

bringing each of the labeled probes in each hybridization reaction within energy transfer distance from one another,

exciting one of the labeled probes in each hybridization reaction, and

detecting electromagnetic radiation released from the other labeled probe as a signal, wherein the presence or absence of a signal for each hybridization reaction is an indicator of the haplotype of the nucleic acid sample.

50. The method of claim 49, wherein each hybridization reaction is performed in a separate vessel.

51. The method of claim 49, wherein the labeled probes are brought within energy transfer proximity of one another using binding partners.

52. The method of claim 51, wherein the binding partners are avidin and biotin.

53. The method of claim 49, wherein the labeled probes are labeled ASOs.

54. The method of claim 49, wherein the method is performed in solution.

55. The method of claim 49, wherein the method is performed on a surface.

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56. The method of claim 49, wherein the nucleic acid sample is an RNA genome.

57. The method of claim 49, wherein the RNA genome is made from cDNA.

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58. The method of claim 49, wherein the nucleic acid sample is genomic DNA.

59. The method of claim 49, wherein the nucleic acid sample is a mitochondrial genome.

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60. A kit comprising:

one or more containers housing:

a first set of ASOs, wherein the first set of ASOs represents two ASOs, each containing one of the two alleles of a first SNP in a polymorphic locus,

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a second set of ASOs, wherein the second set of ASOs represents two ASOs, each containing one of the two alleles of a second SNP in the polymorphic locus, and instructions for performing a hybridization reaction to determine a haplotype from a genomic DNA sample using the first and second sets of ASOs.

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61. The kit of claim 60, further comprising a set of PCR primers for amplifying the polymorphic locus of the genomic DNA sample.

62. The kit of claim 60, wherein the first set of ASOs are fixed to a surface.

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63. The kit of claim 60, wherein the spacer sequence is selected from the group consisting of a poly-T, poly-A, poly-C, and poly-G.

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